UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

UPDATE: Mirtazapine for cancer-associated anorexia and cachexia

Background:

Cachexia is common among patients with advanced cancer. The pathophysiology of cancer cachexia is multifactorial. To date, there is no known intervention that can reverse the progress of cancer cachexia and limited data on pharmacologic therapy for cancer-related anorexia. Few available pharmacologic options include: cannabinoids, megestrol acetate, steroids, stimulants, antipsychotics. Mirtazapine is a noradrenergic and specific serotonergic antidepressant that is also prescribed to improve appetite.

Importance:

Mirtazapine is commonly used in our seriously ill patients to "improve appetite" given its association with weight gain and proposed appetite stimulation when compared to other antidepressants. Prior RCT published in 2021 found that there was no significant difference in appetite for patients with incurable solid tumors prescribed mirtazapine 15mg PO daily (see JPSM 2021 article summary below). This new RCT aimed to assess the effect of mirtazapine and tolerability of mirtazapine 30mg in patients with advanced non-small cell lung cancer (NSCLC) and cancer-related anorexia and cachexia (see JAMA Oncol 2024 article below).

Palliative care clinicians should be aware of this new literature and its implications for clinical practice.

The NEW Literature:

JAMA Oncol. 2024 Jan 11:e235232.

Mirtazapine as appetite stimulant in patients with non-small cell lung cancer and anorexia: A randomized clinical trial

Objective: To assess the effect of mirtazapine on appetite and energy consumption in patients with advanced NSCLC

Methods: Double-blind, placebo-controlled randomized trial

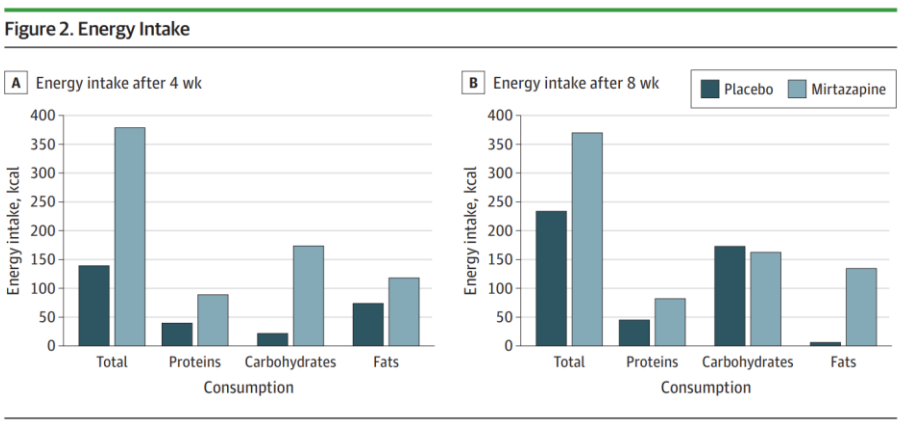
- Mirtazapine 15mg x 2 weeks, increased to 30mg until week 8 or placebo given for same duration

Outcomes:

- Primary: Appetite assessed by Anorexia Cachexia Scale (range 39-156 points) and energy intake (dietary parameters evaluated at baseline, 4 weeks, and 8 weeks)
- Secondary: health-related quality of life (HRQL) and safety

Results: N= 86; n=43 mirtazapine and n=34 placebo; mean age: 63.5 ± 11.2 years, 57.7% Female; 90.2% had ECOG of 1, follow up analysis included 31 patients in mirtazapine and 27 patients in placebo arm

- Appetite score significantly increased in both groups at weeks 4 and 8 by 11 and 12 points in placebo and mirtazapine group respectively ($p < 0.001$) although no significant difference between groups ($p = 0.34$)
- Significant increase in energy in both groups, 31.5% increase in mirtazapine group versus 17.2% increase in placebo group ($p=0.19$ between groups)
- Mirtazapine group had significant increase in proteins and fats intake, placebo group had significant increase in carbohydrate intake; between groups, significant higher increase of fats consumption in mirtazapine group versus placebo ($p=0.02$)



- No difference in weight or body mass in either group at week 8
- After 8 weeks, sarcopenia was identified in the placebo group in 24 participants (82.8%) and 20 participants (57.1%) in mirtazapine group ($p=0.03$)
- HRQL improved from baseline in both groups and significant improvement in anxiety/depression scale in mirtazapine group at both time points
- Mirtazapine was generally well-tolerated; prevalence of hematologic and nonhematologic adverse events was similar between groups except for higher prevalence of grade 1 or higher leukopenia at 8 weeks in mirtazapine group

Discussion:

- No differences in appetite, weight or body mass despite higher doses (30mg) of mirtazapine
- Energy intake increased including high-quality macronutrients which may be a first step to stop unintentional weight loss and stability or increase of body weight
- Small sample size, high dropout rates, which could have resulted in false-positive study results

Conclusion: "…there was no difference in appetite scores in all patients who received mirtazapine or placebo, but the mirtazapine group had a significant increase in energy intake through the 4- and 8-week follow up, mainly fat intake, which is a better and crucial source of energy. The addition of mirtazapine in the treatment of patients with advanced NSCLC and anorexia may help these patients achieve their energy requirements and improve health related quality of life, specifically emotional and cognitive functioning."

CLINICAL PEARL: Mirtazapine is not likely better than placebo in improving appetite, although may improve energy intake for patients with advanced cancer and ECOG of 1.

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Previous Literature:

J Pain Symptom Manage. 2021 May 26;S0885-3924(21)00369-9.

Mirtazapine in cancer-associated anorexia and cachexia: A double-blind placebo-controlled randomized trial.

Objective: To determine the efficacy and tolerability of mirtazapine in patients with incurable solid tumors with cancer-related anorexia and cachexia

Methods: Double-blind, parallel-group, placebo-controlled randomized trial

- Mirtazapine 15mg PO QHS for 28 days (having option to continue for another 28 days), placebo given for same duration

Outcomes:

- Primary: Change in appetite (0-10 scale)
- Secondary: Change in quality of life, fatigue, depressive symptoms, body weight, lean body mass, handgrip strength, inflammatory markers, adverse events, survival

Results: N= 100 (per-protocol analysis) ; N=113 (intention to treat analysis) incurable cancer patients with cancer-associated anorexia and cachexia

- Efficacy:
  - Appetite score increased significantly from day 0 to day 28 in mirtazapine arm by 2 points as well in the placebo arm by 1.5 points on a 0-10 scale. No significant difference in change from baseline to day 28 between treatment arms.
- Safety:
  - No significant difference between arms in change of all other outcome measures, except for HADS-depression score which was higher in the placebo arm at day 28 (higher score indicates worse depression)
  - Adverse effects encountered more often in the mirtazapine arm including sleepiness, hand tremors, visual hallucinations, and abnormal dreams

Discussion:

- Positive anti-depressant effects and increased somnolence in mirtazapine group can continue to support mirtazapine's use for depression and insomnia
- Some patients did not tolerate mirtazapine and discontinued it because of undesirable adverse effects of somnolence/hallucinations

Conclusion: Mirtazapine 15mg is no better than placebo in improving the appetite of incurable solid tumor patients with cancer-associated anorexia and cachexia

Maria's thoughts:

- 2021 study limited mirtazapine to 15mg, and 2024 study increased to 30mg without a difference on appetite compared to placebo. I will continue to hesitate on calling mirtazapine an appetite stimulant based on our available data
- Progression of depression was less with mirtazapine, which is good, considering it is an antidepressant. I wonder if general improvement in mood leads to continued, sustainable energy intake over time for our patients with advanced cancer
- There was a subset of patients with dysgeusia. This may have limited appetite improvement if underlying factor of poor appetite was not addressed with treatment utilized
- Most patients enrolled in the 2024 study had ECOG score of 1. I am left wondering how this data would apply to our patients with ECOG >1. I am not sure we can extrapolate this data to a more deconditioned population…

Bottom Line:

- Address underlying issue contributing to poor appetite, if applicable/possible
- Treating depression (or one of the possible underlying causes of poor appetite) could improve poor appetite or sustain energy intake over time, possibly delaying weight loss related to cancer progression
- There may be a role to utilize mirtazapine earlier in the disease trajectory (ECOG 1) to sustain energy intake (even in our population without an official diagnosis of depression)…?

CLINICAL PEARL: Mirtazapine is not likely better than placebo in improving appetite, although may improve energy intake for patients with advanced cancer and ECOG of 1.